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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,342	ABDUL-AHAD ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/6/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group II, claims 15-16, drawn to a method for treating a patient for multiple sclerosis comprising administering a pharmaceutical composition in the reply filed on 12/13/2006 is acknowledged. The traversal is on the ground(s) that searching Group I and II will not be unduly burdensome. This is not found persuasive because a pharmaceutical composition comprising interferon beta along with treating multiple sclerosis could also be used to treat proliferative, viral and other immune related diseases, which have different etiologies. In addition, the recitation "for treatment of multiple sclerosis" adds no patentable weight to the composition. Further, the restricted groups are classified in different class and subclass. Therefore, the searches of the different groups will not be coextensive for reasons stated above and would constitute undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL. Thus, claims 15 and 16 are examined. Claims 1-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group I, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/13/2006.

Drawings

2. The drawings filed 4/01/2004 are acknowledged.

Information Disclosure Statement

3. The IDS's submitted on 7/06/2005 has been considered.

Specification

4. The use of the trademark Betaseron, Betaferon, Avonex Rebit, Antegren and Natazulimab etc. have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Objections

5. Claim 15 is objected to because of the following informalities: Applicant is required to write in the limitations of claim 1-1 into claim 15. For examination purposes the Office is reading the limitations of claims 1-11 into claim 15.

Claim 16 is objected to because it is depended on a composition claim (method claim dependent on a composition claim).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6a. Claim 16 is rejected, as being vague and indefinite in reciting that claim 16 is dependent on claim 13. Since claim 13 is drawn to compositions it is not clear how a method claim may depend on a composition claim that does not recite any methods. Further, because no methods are recited in claim 13, the dependent claim 16 drawn to methods is vague and indefinite.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7a. Claims 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The claims are drawn to a method of treating a patient for multiple sclerosis comprising administering to a patient human interferon-β mutein.

The specification discloses interferon-β substitution at wild-type position 17 (C17S) and the deletion of the N-terminal methionine of the human polypeptide (see page 13, lines 9-20). This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible muteins. Applicants have claimed a genus of polypeptides that have no common function. Interferon-β has antiviral effects, immunomodulatory effects and anti proliferative effects etc. (see page 2, lines 8-10). It is not clear what substitutions of the mutein will retain common functions. It is also not clear how the changes to the polypeptide would affect the glycosylation.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, not even the partial structure in the form of a recitation of SEQ ID number and possible amino acid changes present. In addition, there is no identification of any particular portion of the structure that must be conserved. The claims as written, however, encompass interferon-β mutein sequences

which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims15 and 16. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of isolated interferon-β polypeptide with substitutions for example, at wild-type position 17 (C17S) and the deletion of the N-terminal methionine the skilled artisan cannot envision all the detailed chemical structure of the claimed mutein polypeptides, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the isolated interferon-β polypeptide with substitution at wild-type positions 17 (C17S) and the deletion of the N-terminal methionine but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors

were in possession of various mutein polypeptide sequences set forth in claims 15 and 16.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

7b. Claims 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for C17S mutein of interferon-β, with the deletion of the N-terminal methionine (see page 3, lines 19-25 of the specification), the disclosure does not reasonably provide enablement for all interferon-β mutein polypeptides contemplated. In addition, it is also unclear what activity if any will be associated with the specific interferon-β muteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a patient for multiple sclerosis comprising administering to a patient human interferon-β mutein.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Despite knowledge in the art for producing muteins of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function(s) of the interferon-β mutein claimed. Furthermore, detailed information regarding the structural and functional requirements of the disclosed mutein protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions

may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The instant disclosure fails to disclose which if any functions of the interferon-β activities will remain or required after the mutation of the polypeptide. It is also unclear what are functions that will be enhanced following the glycosylation of interferon-β. Therefore, predicting which variants would retain the functions of the protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation

would be required to generate changes/modifications contemplated and yet retain the function of the proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of the polypeptide sequences encompassed by the invention of claims 15 and 16. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 15 and 16 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

8.The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8a. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gottesman (abstract published 3/2003, Reference 8 in PTO1449 of 7/06/2005) as evidenced by Giovannoni (2002).

The claims are drawn to a method of treating a patient for multiple sclerosis comprising administering to a patient human interferon-β mutein.

Gottesman teaches the administration of 500μg of Betaseron to treat multiple sclerosis. The Betaseron is a human interferon-β1b mutein with cysteine at position 17 changed to serine (C17S) as evidenced by Giovannoni (2002). The Giovannoni reference also evidences that Betaseron lacks the N-terminal methionine. Therefore claims 15 and 16 are anticipated by Gottesman (abstract published 3/2003, Reference 8 in PTO1449 of 7/06/2005) as evidenced by Giovannoni (2002).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9a. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gottesman (abstract published 3/2003, Reference 8 in PTO1449 of 7/06/2005) as evidenced by Giovannoni (2002) in view of Shirley et al. (6, 887, 462).

The claims are drawn to a method of treating a patient for multiple sclerosis comprising administering to a patient human interferon-β mutein (HSA free).

Gottesman teaches the administration of 500μg of Betaseron to treat multiple sclerosis. The Betaseron is a human interferon-β1b mutein with cysteine at position 17 changed to serine (C17S) as evidenced by Giovannoni (2002). The Giovannoni reference also evidences that Betaseron lacks the N-terminal methionine. However, the Betaseron preparation contains human serum albumin. Claim 11 whose limitation is read into claim 15 does not include human serum albumin in the pharmaceutical composition.

Shirley et al. disclose interferon-β pharmaceutical compositions that are HSA free (column 2, lines 15-18). Shirley et al. each that, the use of HSA has drawbacks because HSA (a product of human blood) carries with it the potential introduction of human viruses such as HIV and HCV (column 2, lines 1-2). Shirley et al disclose that

introduction of HSA into the formulation also interferes with the ability to properly determine the stability of interferon-β in the formulation (column 2, lines 3-5). Furthermore the reference teaches that, interferon-β is a protein that exhibits aggregate formation when prepared in pharmaceutical compositions, and hence the amount of this protein in its monomeric biologically active state is compromised during storage of these compositions(column 2, lines 8-12). Shirley et al. also teach that aggregate formation by a polypeptide such as interferon-β during storage of a pharmaceutical composition can adversely affect biological activity of that polypeptide, resulting in loss of therapeutic efficacy of the pharmaceutical composition (column 2, lines 12-15). In addition, the reference teaches that, aggregate formation may cause other problems such as blockage of tubing, membranes, or pumps when the interferon-β pharmaceutical composition is administered using an infusion system (column 2, lines 17-20). Furthermore Shirley et al. teach that injection of a pharmaceutical composition comprising the aggregated form of a protein has the potential for generating an immunogenic reaction to the aggregated protein (column 2, lines 20-23).

Therefore, it would have been *prima facie* obvious at the time of the invention to modify the treatment methods of the Gottesman (2003) to treat multiple sclerosis as taught by the Shirley et al. using the therapeutic compositions of interferon-β that is HSA free. One of ordinary skill in the art would have been motivated to use the study methods of Gottesman (in the doses) to treat multiple sclerosis by administering interferon-β1b that is HSA free because Shirley et al. disclose that interferon-β that is HSA free avoids the potential for the introduction of viruses, avoids aggregate formation

and avoids the potential for generating an immunogenic reaction to the aggregated proteins. Further, there is reasonable expectation of success because Gottesman study teaches that interferon-β1b can be used to treat multiple sclerosis. Therefore, the instant invention is *prima facie* obvious over Gottesman (abstract published 3/2003, Reference 8 in PTO1449 of 7/06/2005) as evidenced by Giovannoni (2002) in view of Shirley et al. (6, 887, 462).

Conclusions

10. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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JS
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